Indian Journal of Biochemistry & Biophysics
Vol. 58, April 2021, pp. 118-126

**A Review**

# Bio-engineering and bio-design of new generation bioresorbable implants

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*Received 28 December 2019*; *revised 30 May 2020*

Biomaterials play a major role in enhancing the quality, performance and longevity of human life. With the technological advancements in biomedical and material processing, quite a number of biomaterials are being synthesized with properties desirable for various biomedical applications. Among these, bioresorbable materials are the new class of Biomaterials. Bioresorbable materials can be used mainly in orthopaedic, cardiovascular, dental and tissue engineering applications. The potential bioresorbable materials identified were Magnesium alloys, Iron and Zinc alloys. However, there are certain issues with these bioresorbable materials for their application as implants. The current review presents the potential, physiological behavior and problems of Magnesium alloy. The biological performance of Magnesium alloys under different processing methods such as alloying, surface modification and bulk processing was discussed. This review may be a guide for new researchers to identify suitable processing method for Magnesium alloy.

**Keywords**: Biodegradation, Biomaterials, Extrusion, Femoral condyle, Femoral diaphysis, Implants

## Introduction

A biomaterial can be a natural or synthetic material, designed and engineered to interact with the human physiological system. The conventional biomaterials were stainless steel (SS) alloy, cobalt-chromium (Co-Cr) alloy, and titanium (Ti) alloy[1]. Table 1 shows the properties and applications of conventional biomaterials. Stainless steel is one of the commonly used biomaterial in designing human implants. SS-316L possesses good ductility, work harden ability , and fatigue property[2].However, few properties that restrict the application of SS-316 L for different implants were lack of bio-functionalities, anti-fouling properties, inability to integrate with the human tissues consistently, and low blood compatibility[2]. This leads to the failure of stainless steel implants. Titanium alloys were known for low density, high mechanical strength and corrosion resistance[3]. Also, Titanium alloys possess excellent biocompatibility, form stable surface oxides and thus, exhibit bio-inertness. However, processing of Titanium alloys is quite difficult because of the low hardening coefficient[3]. In addition, the corrosion products of Titanium alloys produce high toxicity in the body[3]. Cobalt-chromium alloys were commonly used in designing metal-on-metal hip re-surfacing joints because of biocompatibility, high corrosion resistance, and low wear resistance. Although Cobalt-chromium alloys possess good mechanical properties, they were difficult to process[4]. Also, the leaching of metal ions such as chromium, nickel, and cobalt into the bloodstream reduces the biocompatibility of cobalt-chromium implants by prompting undesirable immune reactions[5,6].

With the limitations of existing traditional metallic implant materials[7], a new generation of biomaterials, called bioresorbable materials was being synthesized. Bioresorbable materials can be applied in orthopedic , cardiovascular, dental, and tissue engineering applications[8]. Bioresorbable materials can be a scientific breakthrough in the biomedical industry. Not every material can be called as bioresorbable. The desirable features essential for bioresorbable material were presented in (Table 2). Bioresorbable implants degrade gradually and will be replaced by newly formed tissue, unlike traditional implants. Ideally, the biodegradation rate must be equivalent to the new tissue forming rate. One of the potential bioresorbable materials identified was Magnesium alloy [9]. Table 3 shows the list of properties and applications of Magnesium alloy. However, there are certain issues with Magnesium alloy for application as implants. The current review presents the potential, physiological behavior, and problems of Magnesium alloy. The biological performance of Magnesium

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Table 1 — Properties and applications of conventional biomaterials

| Material | Density (g/cc) | Yield Strength (MPa) | Ultimate Strength (MPa) | Young's Modulus (GPa) | Application status | Applications | Ref |
|---|---|---|---|---|---|---|---|
| Bone | 1.75 | 30-70 | 70-150 | 15-30 | - | - | 7 |
| SS 316L | 8.03 | 221-1213 | 586-1351 | 200 | In use | Total hip replacements and temporary devices | 8,9 |
| Pure Ti | 4.51 | 485 | 760 | 110 | In use | Dental implants, cardiovascular and total hip replacements | 10 |
| Ti-6Al-4V | 4.43 | 795-1034 | 860-1103 | 101-120 | | | |
| Co-Cr | 8.3 | 448-1606 | 655-1869 | 210-253 | In use | Load-bearing implants, total joints replacements, dental implants, femoral stems, removable partial dentures | 11 |

Table 2 — Desirable features for a bioresorbable material

| Feature | | Characteristics |
|---|---|---|
| Biodegradable | ✓ | Degradable by human biological processes |
| | ✓ | Controlled degradation to complement tissue growth |
| Biocompatible | ✓ | Non-toxic degradation products |
| | ✓ | Avoiding immune rejection |
| | ✓ | Ability to form their own extracellular matrix by invading the host cells |
| Bioactive | ✓ | Ability to interact and bind to host tissue |
| | ✓ | Stimulate cell ingrowth and attachment |
| Mechanical integrity | ✓ | Elastic, compressive and fatigue strength equivalent to host tissue |
| | ✓ | Maintaining structural integrity till the service life |
| | ✓ | Flexibility in customized fabrication on case to case basis |

Table 3 — Properties and applications of Magnesium alloy

| Material | Density (g/cc) | Yield Strength (MPa) | Ultimate Strength (MPa) | Youngs Modulus (GPa) | Application status | Applications | Ref |
|---|---|---|---|---|---|---|---|
| Bone | 1.75 | 30-70 | 70-150 | 15-30 | - | - | 7 |
| Pure Mg | 1.74 | 20 | 90-110 | 45 | Animal Test | Biodegradable orthopedic implants | |
| AZ31 | 1.78 | 171-303 | 241-365 | 45 | | | |

(Mg) alloys under different processing methods such as alloying, surface modification, and bulk processing was discussed.

## Magnesium

Magnesium alloys can be considered as a revolutionary biomaterial for temporary orthopedic implants, because of its high specific strength, good biodegradability, biocompatibility[10], bioactivity[11], and osteopromotive property[12]. Figure 1A-D shows the several bone fixation devices made up of Magnesium alloys[13]. Bone fixation device generally includes a bone plate, bone rod, bone screw, bone pin , and so on, which supports the damaged bone physically and helps in the regeneration of new tissues[14]. The type of bone fixation device was decided based on the severity of bone fracture[13]. Figure 1E shows one case of bone fixation device implanted in the foot[13]. From Table 3, it can be observed that Magnesium alloys have Young's modulus equivalent to human bone. This can reduce the stress shielding effect at the bone-implant interface during load transfer[12]. Owing to attractive degradation characteristics[15], Magnesium alloys degrade gradually and allows the restoration of defect/damaged bone tissue, thereby achieving their clinical purpose as temporary supports perfectly. Hence, the secondary operation can be eliminated, unlike the conventional biomaterials with no degradability. The post-implant treatment can be simplified with a great comfort at a low cost. Also, the degradation product doesn't induce any toxicity in the human body. Additionally, the new bone generation at the periosteal region will be promoted because of the osteopromotive property of Magnesium alloy.

## The potential

Magnesium is the fourth prevalent mineral in the human biological system, and plays a vital role in the generation of soft tissue and bone. The recommended daily allowance of Mg is 250-350 mg for a healthy adult[16]. However, excessive Magnesium was permissible as it can be dispatched through the circulatory system and finally flushed off through urine, thereby avoiding any adverse effects. Tables 4 & 5 show the benefits and limitations of Magnesium, respectively. Despite many advantages, there are few limitations that constraint the application of Magnesium in the biomedical field.

## Physiological degradation

The standard reduction potential of Magnesium was −2.37 V, the lowest of all engineering metals. The electrochemical reactions were given by Eqs. 1 & 2. Eq. 1 refers to the oxidation of Mg to $Mg^{2+}$ ions. Eq.2 refers to the reduction of $H_2O$ to$OH^-$ ions. Eq. 3 refers to the chemical reaction of $Mg^{2+}$ ions and

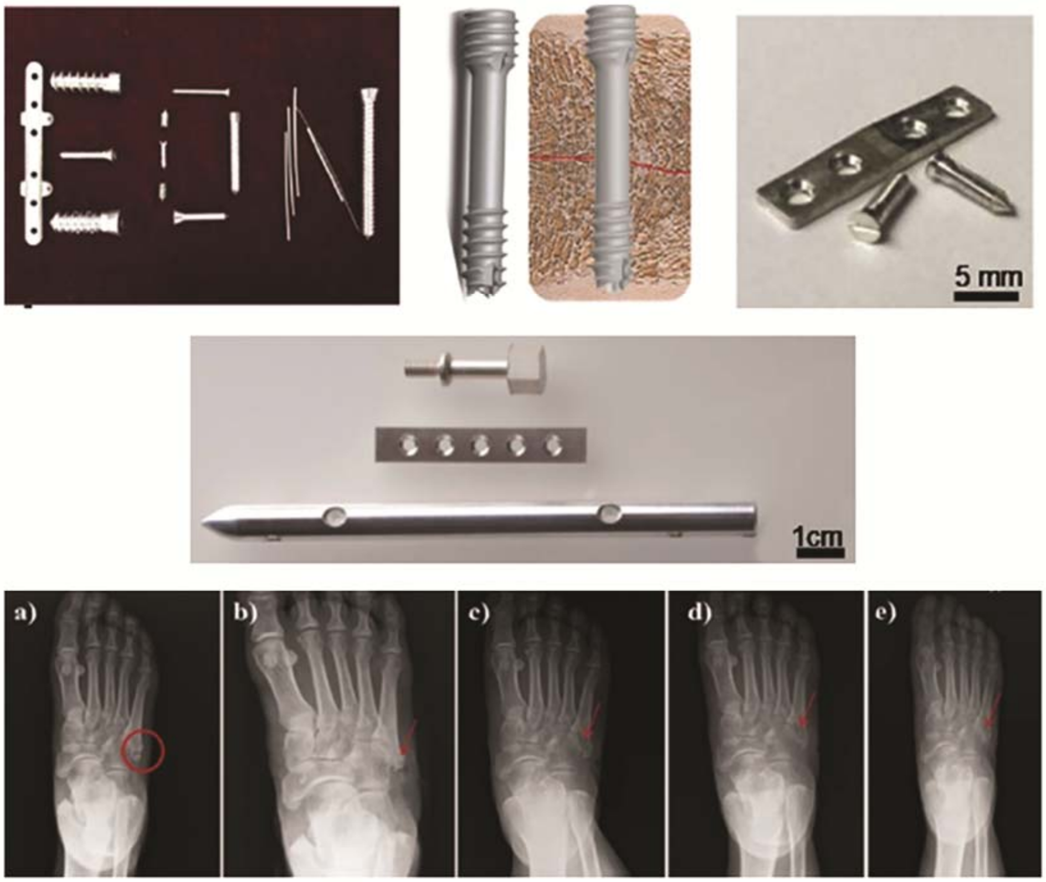


Fig.1 — (A-D) Bone fixation devices such as plates, rods, screws, pins[16]; and (E) one case of bone repair application[16]

Table 4 — Benefits of Magnesium

| Benefits | Characteristics | Details |
|---|---|---|
| Strength-to-weight ratio | High | Strength-to-weight ratio was 130 kNm/kg approximately [7] |
| Density | Low | Density (1.738 g/cc) ;lower than Ti (ρ= 4.5 g/cc) and Fe (ρ=7.9 g/cc)[7] |
| Stress shielding | Less | Implant strength will be almost equivalent to bone[16] |
| Machinability | High | Ease of machining and high dimensional accuracy[11] |
| Damping capacity | High | Ability to absorb energy of any metal[18] |
| Degradation | Good | Degrades completely and can help human body metabolism by providing Mg ions[16] |
| Biocompatibility | Good | Allows host cells to invade and grow for new tissue formation[16] |

Table 5 — Limitations of Magnesium

| Limitations | Characteristics | Details |
|---|---|---|
| Elastic modulus | Low | Due to lower elastic modulus, Mg implants may not sustain the load without deformation[19] |
| Degradation | Rapid | Mg implants were expected to degrade at the rate of bone re-modeling. But currently, Mg is degrading at higher rates[7] |
| Hydrogen evolution | high | $H_2$ gas accumulates at the surrounding soft tissues[16] |

$OH^-$ ions to precipitate as $Mg(OH)_2$. As the equilibrium constant of Eq. 3 is relatively low, $Mg(OH)_2$ forms at high pH values.The chemical reaction in Eq. 3 primarily occurs at the local supersaturation of the $Mg^{2+}$ and $OH^-$ ions. Eq. 4 refers to the overall reaction with Eqs. 1-3 being its basic reactions. Here, the primary reactions *i.e* Eqs. 1-3 occur rapidly and were in close proximity with each other. Mg surface consists of reaction sites where the primary reactions *i.e* Eqs. 1-3 occur, which results in the formation of $Mg(OH)_2$. Hence, the degradation of Magnesium is rapid with high degradation rates[17].

$$Mg(s) \rightarrow Mg^{2+}(aq) + 2e^-(\text{anodic reaction})\ E^o = -2.37\ V \quad \ldots (1)$$

$$2H_2O(aq) + 2e^- \rightarrow H_2(g) + 2OH^-(aq)(\text{cathodic reaction})\ E^o = -0.82\ V \quad \ldots (2)$$

$$Mg^{2+}(aq) + 2OH^-(aq) \rightarrow Mg(OH)_2(s)\ (\text{product formation})\ pH = 11.2 \quad \ldots (3)$$

$$Mg(s) + 2H_2O(aq) \rightarrow Mg(OH)_2(s) + H_2(g)\ (\text{overall reaction}) \quad \ldots (4)$$

## Processing Methods

To address the issues related to Magnesium for orthopedic applications, different processing methods have been adopted[21]. The three major methods are (i) Alloying, (ii) Surface modification, and (iii) Bulk processing. The subsequent sections explain the potential of each processing method to increase the application range of Mg in temporary implants.

## Alloying

Alloying is being performed on Magnesium to enhance the mechanical properties[21] and corrosion performance by precipitation hardening, grain-refinement, and solid solution strengthening[22]. The alloying element selection in developing biodegradable and biocompatible Magnesium alloys were shown in (Fig. 2). The first component is elemental toxicity. The degradation products must be non-toxic in nature and should be absorbable by the surrounding tissues or at least, dissolvable for excretion through kidneys. The second component is the strengthening ability. The third component is the corrosion behavior. The alloying elements of Magnesium should delay or decrease the degradation in any physiological medium. Alloying elements with the equivalent electrochemical potential of Mg (−2.37 V) can reduce the corrosion rate. Otherwise, elements that can form strong intermetallic phases, which have potential similar to Mg can increase the corrosion resistance by avoiding inter- galvanic corrosion. Few such elements were: Ce, −2.48 V; Nd, −2.43 V and Y, −2.37 V[23]. Based on the above considerations of alloy design, a large number of Magnesium alloys were designed and developed to achieve desirable properties. A summary of different Magnesium alloys was represented in (Fig. 3).

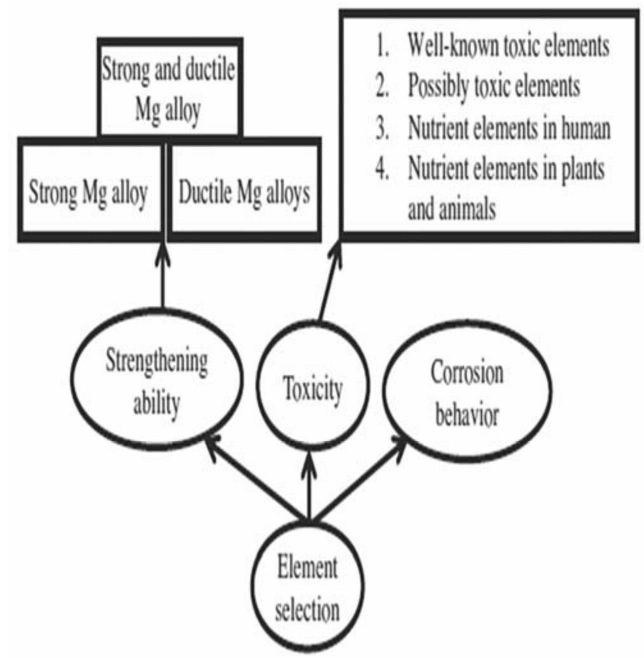

Fig. 2 — Considerations of Magnesium alloy design[22]

The strengthening ability depends on the alloying element chosen. The Mg alloy system was broadly classified as Mg–Al-based, Mg–Zr-based, Mg–Zn-based, Mg– RE-based, and Mg–Si-based alloys. The tensile yield strength and elongation of various Mg alloy systems was presented schematically in (Fig. 4). It was found that Al, Zn, and RE based alloy systems exhibited precipitation hardening inherently due to high solubility of the secondary element in Mg[24]. It was observed that Mg–RE-based alloy system exhibited the highest strength and ductility followed by Mg–Zn-based alloy system. Mg–Zr-based alloy system exhibited the lowest strength and ductility[25]. The alloying elements play a vital role in altering the corrosion behavior of Mg. Typical forms of Mg corrosion witnessed in different physiological conditions

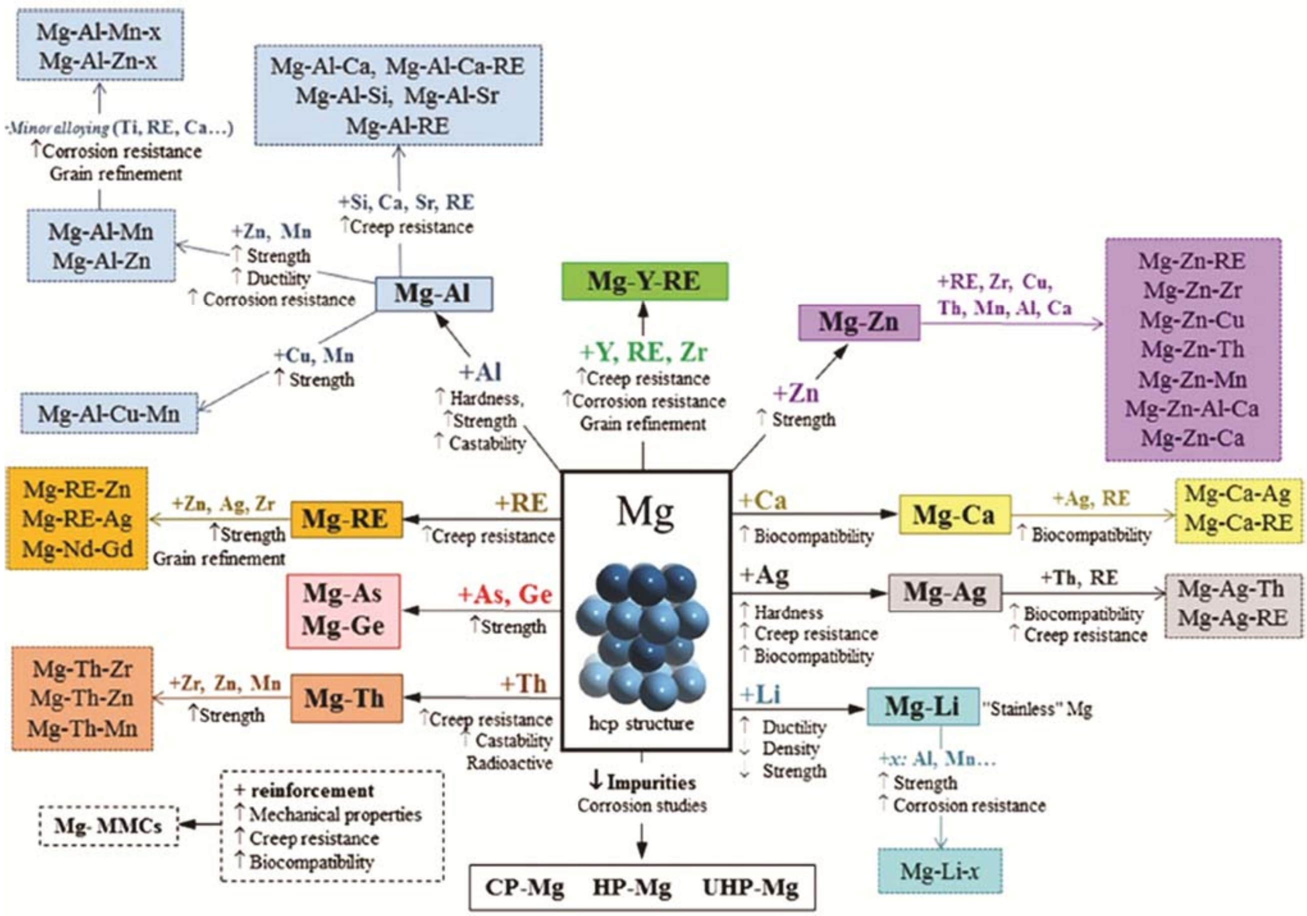


Fig. 3 — Summary of Mg alloy development[24]

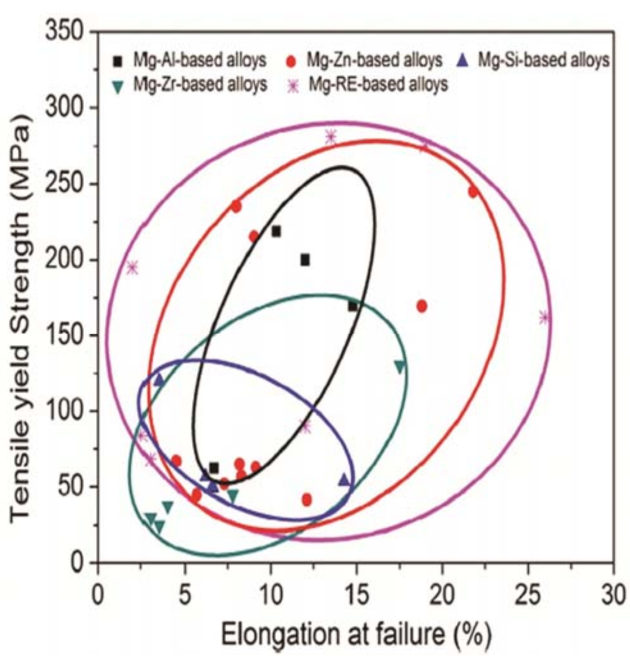


Fig. 4 — Typical yield strength and elongation at failure of biodegradable Mg alloys[22]

were: (i) Galvanic corrosion, (ii) Intergranular corrosion, and (iii) Pitting corrosion. Galvanic corrosion occurs when two different electrochemical potential metals contact with each other in the presence of an electrolyte. Inter-granular corrosion occurs at the grain boundaries due to the precipitation of secondary phases. Pitting corrosion is attributed to the breakdown of the passivation layer in a highly dynamic environment at local sites. The corrosion rates of different Mg alloys in different physiological conditions were presented in (Table 6). It can be observed that the corrosion rate of Mg alloys was found to be lower than the pure Mg. However, there can be a difference in corrosion rates between *in vitro* and *in vivo* studies for the same alloy. This could be due to the limitation in duplication of the exact dynamic behavior of human physiological conditions during *in vitro* studies. Among all, Mg–RE-based alloy system was found to exhibit better corrosion performance followed by Mg–Zn-based alloy system[26].

## Surface modification

Surface modification can play a crucial role in altering the degradation behavior and also in improving the biocompatibility of Magnesium alloys. The different surface modification methods were: (i) Mechanical, (ii) Physical, and (iii) Chemical methods. Commonly deployed mechanical surface modification methods on Magnesium alloys were grinding, milling, cryogenic machining, burnishing, and laser shock peening. The key results of each mechanical surface modification method were depicted in (Table 7). It was observed that the surface integrity was improved drastically with increased compressive residual stress (CRS), surface finish, and microhardness (HV). Laser shock peening of Mg–Ca alloy imparted compressive residual stress[27]. It was found that the high compressive residual stress induced helped to slow down the corrosion significantly. High-speed dry milling on Mg–0.8Ca alloy induced strain hardening effect with increased microhardness up to 12 mm depth. Also, a clean surface was achieved without chip ignition but with a slight flank build-up formation[28]. Cryogenic machining on AZ31B resulted in a grain-refined layer with improved surface integrity features such as higher surface finish, compressive residual stress, grain refinement, and strong basal texture than the dry machining[29]. Ball burnishing on Mg–0.8 Ca alloy improved the surface finish, microhardness, and transformed tensile residual stress to compressive residual stress. The compressive residual stress was induced up to 200 mm depth[30].

Commonly deployed chemical methods on Magnesium alloys were anodic oxidation[34], fluoride conversion[35], alkali heat treatment[36], biomimetic deposition[37], electrodeposition[38], polymer coatings[39], and sol-gel coating[39]. The key results of each chemical method were presented in (Table 8). Chemical coatings produce a thin layer of metal oxide or metal salt on the surface of Mg by chemically bonding. Commonly deployed physical surface modification methods on Magnesium alloys were physical vapor deposition (PVD)[38], plasma-enhanced chemical vapour deposition (PECVD), ion implantation, ion-beam assisted deposition (IBAD) [39] and ion plating. The results of different physical methods were presented in (Table 9). Ion implantation

Table 6 — Corrosion behavior of Magnesium alloys

| Alloy | Duration (Days) | *In vitro* degradation | | | *In vivo* degradation | | | | Ref |
|---|---|---|---|---|---|---|---|---|---|
| | | Degradation rate | Corrosive medium | Method | Degradation rate | Method | Implant site | Animal | |
| Pure Mg | 14 | 1.483 mm/yr | EBSS | Weight loss | 1.03 mm/yr | Volume loss | Ulnae | Rabbit | 24 |
| AZ31 | 14 | 0.670 mm/yr | SBF | Weight loss | 0.735 mm/yr | Weight loss | Subcutaneous | Rat | 25 |
| WE43 | 42 | 0.31 mm/yr | EBSS | Electrochemical | 1.2 $mm^2$ | Weight loss | Femora | Guinea pig | 24 |
| Mg-0.8Ca | 7 | 0.573 mm/yr | EBSS | Weight loss | 0.312 mm/yr | Weight loss | Subcutaneous | Rat | 24 |
| LAE442 | 42 | 6.9 mm/yr | Ocean water | Electrochemical | 1.6 $mm^2$ | Weight loss | Femora | Guinea pig | 25 |

Table 7 — Results of different mechanical methods

| Method | Key findings | Residual stresses | Degradation rate | Ref |
|---|---|---|---|---|
| Laser shock peening | ✓ Tensile residual stress on the surface was transformed to Compressive residual stress<br>✓ Compressive residual stress can delay the degradation rate | Increased up to 1-2 mm depth | Decreased | 27 |
| High-speed dry milling | ✓ Enhanced surface integrity such as surface finish and microhardness can reduce degradation rate<br>✓ Microhardness was increased up to 12 mm depth | Increased | Decreased | 28 |
| Cryogenic machining | ✓ Nano crystalline grain structure was induced with strong basal texture on the surface<br>✓ Surface integrity was enhanced | Increased | Decreased | 29 |
| Ball burnishing | ✓ Tensile residual stress on the surface was transformed to Compressive residual stress<br>✓ Enhanced surface integrity such as surface finish and microhardness<br>✓ Can be ideal for Mg as increase in temperature during burnishing was 5-6°C | Increased Up to 250 µm depth | Decreased | 30 |

Table 8 — Results of different chemical methods

| Method | Key findings | Main layer structure | Layer thickness (µM) | Ref |
|---|---|---|---|---|
| Anodic oxidation | Anodic oxidation at 2-100 V for 3-10 min | MgO | <20 | 31 |
| Flouride conversion | Immersing in 40% HF for 3-168 h | MgF2 | <3 to 200 | 32 |
| Alkali heat treatment | Immersing in alkalized solution and heat treatment at 773 K for 10 h | MgO | <30 | 33 |
| Biomimetic deposition | Immersion for 48h followed by heat treatment at 573 K for 2 h | HA | 300 | 34 |
| Electro deposition | Immersing in acidic electrolyte at 0.4-20 mA/cm$^2$ for 30-80 min at 60-85°C | HA, FHA | 10-20 | 35 |
| Polymer coatings | Dip-coating by saline based PLGA and PLLA | PLGA, PLLA | 20-70 | 36 |
| Sol–gel | Dip-coating followed by heat treatment | HA | 0.45-500 | 37 |

Table 9 — Results of different physical methods

| Method | Key findings | Degradation rate | Ref |
|---|---|---|---|
| Ion implantation | Zn ion implantation with a modified layer | Decreased | 38 |
| IBAD | C–N coating and calcium-phosphate coating of 240 nm and 3 mm thick, respectively | Decreased | 39 |
| PVD, PECVD | High purity coating | Decreased | 40 |

Table 10 — Results of different bulk processing methods

| Method | Material | Implantation site | Animal | Degradation rate (mm/yr) | Ref |
|---|---|---|---|---|---|
| Extrusion | LAE442 | Femoral condyle | Rabbit | 0.31 | 41 |
| Extrusion | Mg–0.8Ca | Transcortical implant in tibia | Rabbit | 1.27 | 42 |
| Extrusion | Mg–6Zn | Femoral diaphysis | Rabbit | 2.32 | 42 |
| FSP | AZ31-nHA | SBF | - | 2.62 | 43 |
| ECAP | AZ31 | Femoral diaphysis | Rabbit | 2.5 | 44 |
| Rolling | Mg–Sr | Marrow cavity | Mice | 1.01 | 44 |

is a process of the bombardment of energetic ions onto the substrate surface layer. Zn–Nd–Zr alloys were implanted with O by ion implantation resulted in a thick oxide layer on the surface[40]. IBAD coating on AZ31 increased the microhardness and Young's modulus significantly and also resulted in a slow degradation rate[40].

## Bulk processing

Altering the microstructure might change the properties of a material. Refining the grain size can be one of the approaches to improve the mechanical integrity and corrosion resistance of Magnesium. Grain refinement can be achieved by bulk processing techniques such as extrusion[41], friction stir processing[42], rolling[43], and equal channel angular pressing (ECAP)[44]. The results of different bulk processing methods were represented in (Table 10). Bulk processing techniques induce grain refinement either by severe or low plastic deformation by introducing stacking faults and high-density dislocations in the microstructure[44]. As a result, defect strengthening and grain size strengthening can be inherently obtained simultaneously.

## Conclusion

The conventional biomaterials that are currently being used for temporary implants were stainless steel alloy, cobalt-chromium alloy, and Titanium alloy. Non-degradable nature is the greatest limitation of conventional metal implants. To overcome such limitations, a new generation of biomaterials, called bioresorbable materials such as Mg was being explored. Mg can be a potential bioresorbable material because of its high specific strength, good biodegradability, biocompatibility, bioactivity, and osteopromotive property. However, the application of Mg for temporary implants was constrained because of rapid degradation, low strength, and hydrogen evolution. To improve the mechanical strength and corrosion resistance, the different techniques employed were alloying, surface modification, and bulk processing. Among all the alloy systems, Mg–RE-based alloy system exhibited the highest strength, ductility, and corrosion resistance followed by Mg–Zn-based alloy system. However, alloying improved the desired properties of Mg to an extent but not up to the application range. Therefore, further processing is required to implement as temporary implants. The major processing methods of Mg alloys were surface modification and bulk processing. The Mg alloys exhibited a wide range of corrosion rates for different processing methods in different physiological conditions. Therefore, further investigations were required to identify the best alloying composition and processing method.

**Acknowledgement**

The authors would like to acknowledge the Department of Biotechnology, National Institute of Technology Raipur, Chhattisgarh, India- 492010 for their support.

**Conflict of Interest**

All authors declare no conflict of interest.

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